DOI: 10.7860/JCDR/2018/34568.11200

Original Article

Anaesthesia Section

Effect of Low-flow Sevoflurane Anaesthesia on Renal Functions in Patients Undergoing Surgery: A Retrospective Study

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ABSTRACT

Introduction: Sevoflurane is a commonly used inhalational anaesthetic agent in India. However, there is limited information on the effect of low-flow sevoflurane anaesthesia on renal function in Indian patients undergoing major surgeries.

Aim: To assess the effect of low-flow sevoflurane anaesthesia on renal parameters in adult patients undergoing elective surgery for more than two hours.

Materials and Methods: This was a cross-sectional, single centre, retrospective study was conducted in the Department of Anaesthesia, Fortis Hospital, Delhi, India (November 2016 to May 2017). Change in serum creatinine and Blood Urea Nitrogen (BUN) values from baseline to postsurgery and number of patients experiencing postoperative glucosuria and proteinuria were recorded. Categorical data are presented using numbers and percentages whereas continuous data are summarised using mean and standard deviation. Statistical difference in the preoperative values of serum creatinine and BUN was evaluated using paired t-test and p-value less than 0.5 was considered statistically significant.

Results: The study included 100 patients (44% males and 56% females) with mean age of 41.3±12.59 years. Mean duration of surgery was 163.3±51.78 minutes. There was no clinically significant difference in the vital parameters after surgery. Serum creatinine (0.77 vs 0.76 mg/dL; p=0.2415) and BUN (11.79 vs 12.26 mg/dL; p=0.2624) did not change significantly after surgery. None of the patients developed proteinuria or glucosuria. There was no report of change in the dose or anaesthetic drug due to intolerance or adverse event caused by sevoflurane.

Conclusion: Low-flow sevoflurane can be safely administered as an anaesthetic agent in elective surgeries among Indian adult patients with normal renal functions.

Keywords: Elective surgical procedure, Inhalation anaesthetic, Renal safety

INTRODUCTION

Sevoflurane, a halogenated inhalational anaesthetic was introduced globally during 1994-95 [1,2]. Because of its favourable pharmacological profile and pleasant smell, today it is one of the most commonly used induction and maintainance inhalational anaesthetic agents in India [2]. Use of low-flow anaesthesia is a common practice in adults because of significantly less wastage of anaesthetic agents, resulting in cost saving for the patients [3]. This is of a particular significance in resource limited countries and settings where patients have to pay out of the pocket for their health services. Closed circuit anaesthesia with inhalation agents also offers environmental benefits [4]. Thus, reducing fresh gas flow reduces both costs and environmental pollution [5]. With these well accepted advantages, use of low-flow sevoflurane is commonly practiced in the Indian settings.

One of the major concerns among anaesthesiologists regarding use of inhaled anaesthetic agents is the potential of renal toxicity [2]. Sevoflurane low-flow anaesthesia administered in closed system is also associated with controversies related to renal toxicity caused by compound A, a degradation product, which has shown renal toxicity in rats [4,6-8]. Compound A is formed by the interaction of sevoflurane with carbon dioxide absorbents in the anaesthesia machine [6]. Sevofluorane degradation is more in lime containing high levels of potassium hydroxide [9]. Generally, sodium hydroxide and potassium hydroxide are used for carbon dioxide binding in absorbers. These agents have been implicated in breakdown of sevoflurane in the canister [10]. Considering this, carbon dioxide absorbants with lesser potential to produce compound A have been introduced in the market [10,11]. A study showed that carbon dioxide absorber devoid of sodium and potassium hydroxide produces minimal compound A [12]. In another study, an absorber devoid of potassium hydroxide, but having calcium hydroxide with sodium hydroxide and calcium chloride also, showed lower compound A concentration with low-flow sevoflurane anaesthesia [11]. Species differences for compound A nephrotoxicity is known. Compound A is toxic in rats, but similar results in dogs and monkeys are not shown [2,7,8]. Similarly, significant association of low-flow sevoflurane anaesthesia with renal toxicity is not shown in human adults. In low birth weight infants, low-flow sevoflurane given as semi-closed inhalation anaesthesia has not shown significant effect on the renal parameters [13]. Limited data exists on overall renal safety and safety of low-flow sevoflurane in Indian patients. The aim of the study was to assess the effect of low-flow sevoflurane anaesthesia on renal function in patients undergoing surgeries for more than two hour duration.

MATERIALS AND METHODS

In this cross-sectional, single centre, retrospective study conducted in the Department of Anaesthesia, Fortis Hospital, Delhi, India (November 2016 to May 2017). Adult patients between 18 to 65 years of age who had under gone an elective surgery for more than two hours in the preceding six months by using low-flow sevoflurane anaesthesia (fresh gas flow less than one liter per minute) were included. All patients had normal preoperative renal functions. Patients with past history of dialysis, renal transplantation or surgery for any renal disorder, those who had undergone an emergency surgery, evidence of use of any contrast media during the surgery, known hypersensitivity to sevoflurane or any other condition that precluded use of sevoflurane were not included. Similarly, pregnant and/or lactating women were also excluded from the study. Medical

records of all patients admitted for surgery were obtained from the Medical Records Department of the hospital and evaluated for the eligibility for inclusion in the study. The administration of general anaesthesia was individualised based on the patient's response. Change in serum creatinine and BUN values from baseline to postsurgery were evaluated for all enrolled patients. Number of patients experiencing postoperative glucosuria and proteinuria were also measured. In addition, the fresh gas flow rate, carrier gases used (O_2 plus air), end tidal concentration of sevoflurane, type of CO_2 absorber used, duration of surgery, type of breathing circuit used (open/closed), inducing agents (other than sevoflurane) used and other anaesthetics, muscle relaxants used were recorded. Approval from Institutional Ethics Committee was obtained before initiation of the study.

STATISTICAL ANALYSIS

Discrete data are summarised using numbers and percentages whereas continuous data are summarised using mean and standard deviation. Statistical analysis was performed using SAS® version 9.2 (SAS Institute Inc., USA). Statistical difference in the preoperative values of serum creatinine and BUN was evaluated using paired t-test at 5% level of significance.

RESULTS

Medical records of 169 patients were screened and 100 patients were included in the analysis. Other 69 (40.83%) patients did not meet the enrollement criteria, hence were considered as screen failures and not included in the study.

Demographic Details

The study included 44 (44%) males and 56 (56%) females. Overall mean age of the population was 41.3±12.59 years. Mean weight and height was 83.9±27.81 kg and 162.7±10.48 cm, respectively.

Medical History and Concomitant Medicines

History of hypertension, diabetes, hypothyroidism, musculoskeletal or connective tissue disorder and asthma was present in 32 (32%), 19 (19%), 16 (16%), 4 (4%) and 3 (3%) patients respectively. History of coronary artery disease, goitre, dyslipidemia, chronic obstructive pulmonary disease, coronary artery bypass and paraplegia after cervical spine surgery was present in one patient each whereas sleep apnoea syndrome, depression and seizures were present in two patients each. Only 2 (2%) patients had significant family medical history, both of hypertension.

A total of 22 (22%) patients were receiving antihypertensive medicines which included amlodipine 6 (6%), telmisartan 6 (6%), metoprolol 3 (3%), olmesartan 2 (2%), valsartan 2 (2%), atenolol 2 (2%) and bisoprolol 1 (1%). A total of 28 (28%) patients were on endocrine medicines which included metformin 8 (8%), levothyroxine sodium 8 (8%), glimepiride 5 (5%), human soluble insulin 3 (3%), vildagliptin 3 (3%), and sitagliptin 1 (1%). Five patients were taking medicines for cardiac disorders which included clopidogrel and acetylsalicylic acid (n=2 each) and atorvastatin (n=1).

Anaesthesia and Muscle Relaxants

The mean duration of surgery was 163.3±51.78 minutes ranging from 122 to 365 minutes. All patients received sevoflurane with dial setting of two or more and fresh gas flow less than one liter per minute in a closed breathing circuit. The mean fresh gas flow rate was 0.9±0.06 liter/minute whereas mean end tidal concentration was 1.8±0.11. A total of 91 (91%) patients received midazolam whereas all patients were administered fentanyl and propofol as inducing agents. Atacurium was used in 99 (99.00%) patients. Sofnolime was used as CO_2 absorber in all patients.

The mean temperature before surgery was 98.34±0.31°F whereas after surgery it was 98.37±0.16°F. Values of mean pulse rate, respiratory rate, systolic blood pressure and diastolic blood pressure before surgery and after surgery are shown in [Table/Fig-1]. There was no clinically significant difference in the temperature, pulse rate, respiratory rate or blood pressure after surgery.

Parameters	First visit: preoperative (n=100) mean±SD	Second visit: postoperative (Next day of surgery) (n=100) mean±SD
Temperature (°F)	98.34±0.31	98.37±0.16
Pulse rate (bpm)	82.78±7.64	83.07±6.84
Respiratory rate/minute	16.46±2.77	15.92±2.26
Systolic blood pressure (mmHg)	126.15±12.24	125.69±11.33
Diastolic blood pressure (mmHg)	77.84±6.77	76.56±7.27

[Table/Fig-1]: Vital parameters.

Renal Function Tests

There was no clinically significant change in serum creatinine values from first visit to second visit. Also, there was no statistical significance in serum creatinine from preoperative visit to postoperative visit (p=0.2415) [Table/Fig-2].

The mean change in BUN from first visit (preoperative) to second visit (postoperative) observed was 0.5 mg/dL. Similarly, no clinically significant change in BUN values from preoperative visit to postoperative visit was observed (p=0.2624) [Table/Fig-2].

Laboratory parameters	First visit: preoperative (n=100) Mean±SD	Second visit: postoperative (Next day of surgery) (n=100) Mean±SD
Mean serum creatinine (mg/dL)	0.77±0.17	0.76±0.21; p=0.2415
Mean BUN (mg/dL)	11.79±4.43	12.26±4.37; p=0.2624
% of patients with glucosuria	0	0
% of patients with proteinuria	0	0

[Table/Fig-2]: Renal safety at different visits.

Safety and Tolerability

There were no reports of change in the dose or anaesthetic drug due to intolerance or adverse event due to sevoflurane. No clinically significant changes in vital signs, physical findings, or other observations related to the safety were recorded in patients in this study. No adverse events were reported in the study. Overall, no clinically relevant significant changes in serum creatinine, BUN, proteinuria or glucosuria were observed post-surgery when compared to pre-surgery laboratory parameters.

DISCUSSION

Although, sevoflurane is a well accepted inhalational anaesthestic agent among the Indian anaesthesiologists, there are some concerns about renal toxicity due to fluoride ions and compound A generated from sevoflurane [14]. In this retrospective study, we evaluated the effect of low-flow sevoflurane on renal functions of patients exposed to wide variety of surgeries lasting for more than two hours. Sevoflurane was administered with dial setting of two or more and fresh gas flow less than 1 L/minute in a closed breathing circuit. Muscle relaxant and inducing agent were used to obtain adequate anaesthesia. The dial concentration of sevoflurane was monitored by vaporizer calibrated specifically for its delivery. The delivered sevoflurane was monitored with anaesthesia gas monitor (Philips IntelliVue GS-M1019A). The administration of general anaesthesia was individualised based on the patient's response.

Overall, low-flow sevoflurane was well tolerated by patients in this study. No significant or new safety signals were detected. A study had reported no change in plasma creatinine level, however with significant reduction in plasma BUN with low-flow desflurane, sevoflurane and propofol [15]. In another study, the percentage of

patients with creatinine increase was not significantly different with sevoflurane compared to isoflurane or propofol in patients with elective coronary artery surgery [16]. In the present study, we did not find clinically significant change in serum creatinine or BUN after low-flow sevoflurane.

The present study observations are different from that of a study conducted by Ebert TJ and Arain SR [15]. In their study, significant increase in urine glucose and protein was observed in all study groups i.e., low-flow desflurane, sevoflurane and propofol and changes were similar in all three groups without the association of anaesthetic concerntation with abnormal renal findings. As changes were observed in all the study groups, the authors suggested role of nonanaesthetic factors such as surgical or postoperative factors for the same. Higher changes after surgeries in central regions indicate role of glomerular capillary haemodynamic effects or surgical stress in postoperative renal changes [15]. In another study, Higuchi H et al., [17] also showed mild and transient proteinuria associated with low-flow sevoflurane, without change in BUN and creatinine in patients without preexisting kidney disease. Renal tubular toxicity and disturbed proximal tubular reabsorption are the described reasons for proteinuria and glycosuria [17]. None of the patients in the present study developed glucosuria and proteinuria after administration of low-flow sevoflurane.

A study comparing renal function after administration of low-flow sevoflurane and isoflurane using biomarkers of tubular damage showed similar effects with both the agents [18]. The results of the study showed that moderate duration low-flow sevoflurane maybe as safe as using low-flow isoflurane. Expsoure to compound A during surgeries of short period (i.e., two to three hours) with sevoflurane anaesthesia do not affect the kidney. Similarly, in surgeries lasting for 10 or more hours, prolonged low-flow sevoflurane has shown to have similar effect on renal parameters as that of high-flow sevoflurane and low-flow isoflurane anaesthesia [19]. In the present study results also showed renal safety of sevoflurane exposure for surgeries lasting for over two hours (mean duration of surgery 163.3 minutes).

Low-flow sevoflurane has also been used in patients with preexisting stable renal insufficiency. In such patients, renal functions are similar with low-flow isoflurane [20]. We enrolled patients with normal renal functions, but effect of low-flow sevoflurane in Indian patients with stable preexisting renal insufficiency can be evaluated in future studies.

Because of interactions of carbon dioxide absorbent and sevoflurane resulting in production of compound A and differences in carbon dioxide absorbents, its choice is also a topic of debate. A study comparing four carbon dioxide absorbents did not show significant differences in renal safety profile [21]. In the present study, sofnolime was used in all patients. A Russian study showed no significant renal injury in healthy patients with compound A level 275 ppm/hour during minimal flow anaesthesia [22]. In the present study, patients had normal renal functions before undergoing surgery. These observations reaffirm the use of low-flow sevoflurane in patients undergoing surgery.

Overall, observations from present study suggest no adverse effect on renal parameters with sevoflurane in Indian patients' undergoing surgery for more than two hours. In humans, the renal cysteine conjugate β-lyase pathway responsible for metabolism of compound A is much less active compared to that in rats. Postulation that if this mechanism is responsible for renal damage, humans may have a lesser potential for risk, is supported by the observations in the present study [6]. We did not evaluate the concentration of compound A, but no significant change in renal functions in patients from present study supports this theory.

LIMITATION

In the present study has some limitations. We did not compare the renal function changes with other inhalational anaesthetic agents. The present study was evaluation parameters were restricted to traditional renal function tests without any biomarkers. Significantly reduced compound A formation is possible with some carbon dioxide absorbants. We did not evaluate or compare the levels of compound A with different carbon dioxide absorbants; hence, it is difficult to conclude whether lack of renal toxicity seen in the present study is result of carbon dioxide absorbant, low-flow sevoflurane itself or both. Use of only one carbon dioxide absorbent in all patients restricted us from comparing effects with other agents. Single centre, retrospective study design and short term follow up limits generalization of findings to all patients. Neverthless, the observations affirm the renal safety profile of sevoflurane and suggests no new safety signal when used in patients with normal renal function tests. Larger, prospective studies are required to confirm these findings.

CONCLUSION

In the present study, administration of low-flow sevoflurane was not associated with any major concerns related to the renal safety. The results of present study suggest that low-flow sevoflurane anaesthesia in patients with elective surgeries lasting for more than two hours is found to be renal safe and can begiven for maintainace of anaesthesia in patients with normal renal functions.

DISCLOSURE

The research funding support was provided by Abbott Healthcare Pvt Ltd. The authors have declared and confirmed that there is no conflict of interest with respect to this authored publication.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. Anant Patil for his support during the process of drafting the manuscript.

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FINANCIAL OR OTHER COMPETING INTERESTS: As declared above.

Date of Submission: **Oct 26, 2017**
Date of Peer Review: **Dec 15, 2017**
Date of Acceptance: **Jan 12, 2018**
Date of Publishing: **Feb 01, 2018**